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Annotation

The Cox model is better than the Fine and Gray model when estimating relative revision risks from arthroplasty register data

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Background and purpose — Analysis of the revision-free survival of knee and hip prostheses has traditionally been performed using Kaplan–Meier analysis and Cox regression. The competing risk problem that is related to patients who die during follow-up has recently been increasingly discussed, not least with regard to the problem of choosing a suitable statistical method for the analysis. We compared the results from analyses of Cox models and Fine and Gray models.

Methods — We used data simulation based on parameter estimates from the Swedish Knee Arthroplasty Register and assessed hypothetical effects of the studied risk factors.

Results — The Cox model provided more adequate results.

Interpretation — The parameter estimates from the Fine and Gray model can be misleading if interpreted in terms of relative risk.

The analysis of arthroplasty data has traditionally been performed using Kaplan–Meier (KM) analyses or Cox regression models (Cox) for adjustment of differences in the distributions of age and sex. The purpose is typically to estimate, in a cohort of patients with arthroplasties, either the absolute (KM) or the relative revision risk (Cox) for certain factors among patients with different lengths of follow-up, a consequence of patients' varying inclusion (operation dates) in the studied cohort.

At the end of follow-up, which usually occurs on the same date for the entire cohort, unrevised patients, who have had their implants for varying lengths of time, are censored. However, some unrevised patients may have been censored prior to this because of emigration or death.

Both the KM and Cox methods are based on underlying assumptions regarding the censoring. The KM method requires non-informative censoring, i.e. that the distribution of censorship times does not provide any information regarding implant survival times and vice versa. Censored patients should have the same revision risk as non-censored patients. This is clearly not the case with patients who are censored because of death.

The Cox method requires independent censoring, i.e. that censored patients are "representative" of those under observation at the same time, conditional on covariates at each point in time (Andersen et al. 1992).

In other words, censoring is independent if it is random within any subgroup defined by the covariates. Independent censoring is thus less restrictive than non-informative censoring.

Both the non-informative and the independent censoring assumptions are incompatible with the censoring of events that preclude the studied event. Such events are known as competing events. Patient death is a typical competing event when studying implant revision.

When estimating revision risk, 2 different estimates can be defined depending on whether or not death as a competing event has been accounted for in the analysis: The net revision risk can be defined as the revision risk estimate in a hypothetical world where all patients live until they experience revision. Competing risks are simply assumed to be eliminated. An estimate of the 10-year revision risk corresponds to the risk that a patient can expect if he or she lives that long.

The crude revision risk can be defined as the revision risk in the real world where some patients die during follow-up without being revised. The actual revision risk will thus be

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True (simulated) and estimated values when comparing the revision-free survival of 2 different hypothetical prostheses types and including age and sex in the analysis

Variable	RR	95% CI
Values used in the simulation		
Prosthesis	2	–
Age	1	–
Sex	1	–
Estimated values using a Cox model		
Prosthesis	2.05	2.01–2.08
Age	1.00	1.00–1.00
Sex	1.00	0.98–1.02
Estimated values using a Fine and Gray model		
Prosthesis	2.03	2.00–2.07
Age	0.99	0.99–0.99
Sex	0.86	0.85–0.87

lower than it would have been if these individuals had lived long enough to be revised.

The estimation of crude revision risks focuses partly on other statistical methods than those previously used. The cumulative incidence method is usually used for estimating absolute crude risks and the Fine and Gray method when estimating relative crude risks (Gillam et al. 2010, 2011, Lacny et al. 2015, Maradit Kremers et al. 2016, Graw et al. 2009, Jameson et al. 2015).

Until recently, arthroplasty register reports have mainly presented net revision risks. After discussion in scientific journals, crude revision risks are now also presented (Gillam et al. 2010, 2011).

While the cumulative incidence method has not been a matter for much debate, the Fine and Gray models have been criticized on the grounds that their parameter estimates, which describe the relationship between risk factors and revision risk, are difficult to interpret (Andersen et al. 2012, Dignam et al. 2012). We compared the outcomes from the traditional Cox models with the results from the more recently introduced Fine and Gray models when analyzing relative revision risks with arthroplasty register data.

Methods

We used random samples from the Swedish Knee Arthroplasty register to estimate the empirical survival distributions (the time from the primary operation to death) of each sex and 5-year age class with help of the R library *fitdistrplus*, and we used the estimated parameters to simulate death as a competing event with fictitious revision rates. When estimating survival we assumed that this was distributed according to a Weibull distribution. We also assumed that the revision-free survival for 2 fictitious prosthesis types was distributed according to exponential distributions yielding 10-year revision risks similar to what has been observed empirically, i.e. in the magnitude of 4–8%. The computing of simulated data was performed using the R library *survsim*.

The simulated data were then analyzed in Stata version 14.2 (Stata Corp LLC, College Station, TX, USA) using a Cox regression model and a Fine and Gray regression model with 1 binary indicator for the 2 fictitious implant types (0–1) and another binary indicator for women and men (0–1). Age in 5-year classes was included as a discrete variable. The simulation of data was repeated in cycles of 500 simulations and analyses.

The hazard ratios estimated from the simulated data were then compared with the parameter values used in the simulations.

Results (Table)

While both models provided reasonably good estimates of the relative revision risk of prosthesis type and age, the Fine and Gray model substantially underestimated the revision risk for men.

Discussion

One explanation for the unbiased estimates from the Cox model in spite of the competing risk problem is that the censoring, at least in these simulations, depends on the parameters of the model, and that the Cox model is based on conditioning on observed values of censoring. The censoring distributions then do not enter the partial likelihood and therefore do not introduce bias (Broström 2001).

The reason for the underestimation of the male revision risk with the Fine and Gray model is the way this model takes the competing risk into account. A covariate (sex), which does not affect the primary event (revision) in itself, but is associated with the competing event (death), will appear to be associated also with the primary event, the revision risk. This problem has also been discussed in other publications (Szychowski et al. 2010, Dignam et al. 2012).

A clinically more serious problem can be envisaged if 2 prosthesis types with identical revision risks are allocated differently to patients with different mortality patterns, for example because of comorbidities. A Fine and Gray model would then have given the false impression that the revision risks of these prosthesis types differed. The phenomenon would not occur with a Cox model.

The differences in results between the 2 models depends on the different model formulation. The Fine and Gray model answers a slightly different question than the Cox model. The issue addressed by the Fine and Gray model refers to the pattern of actually performed revisions of men and women, not (as with the Cox model) to the revision risk

that could be expected for a patient living long enough. The latter information is important for rational clinical decision-making vis-à-vis individual patients. The former information is relevant when planning economic projections and allocation of resources.

Furthermore, analyzing death as a competing event makes it difficult for orthopedic surgeons and patients to relate the results to previously published implant survival studies, which use the KM or the Cox method. It is important that publications intended for the orthopedic community clearly provide the reason for using competing risk analysis and explain the differences in results as compared with the more conventional KM and/or Cox methods.

In conclusion, we recommend using the Cox model when estimating relative revision risks using arthroplasty data. If Fine and Gray models are used, the authors should carefully consider the interpretation of the results in relation to the mortality patterns.

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